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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/389,000	Applicant(s) AFAR ET AL	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-12,14-50 and 53-77* is/are pending in the application.

4a) Of the above claim(s) *5-12,14-50 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 1-4, 13, 51 and 52 and adds new claims 54-77, which are related to claims 1-4, 13, 51 and 52 and are not new matters.

Applicant's election of species amino acids 140-154 of SEQ ID NO:2 in Paper No. 11/13/01 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 54-77 are examined in the instant application.

The following are the remaining rejections.

SEQUENCE RULE COMPLIANCE

Rejection remains because the amino acid sequence recited on the first line of page 36 is not accompanied with a sequence identification number.

REJECTION UNDER 35 USC 101, UTILITY

New claims 54-77 are rejected under 35 USC 101 pertaining to lack of a specific and/or substantial utility remains for reasons already of record in paper No.10.

Applicant asserts that a proper utility inquiry addresses whether one would find it more likely than not that PHELIX protein is expressed in cancerous tissues but not in normal tissues, except for testis, given the mRNA expression data disclosed in the Application. The Office has taken a position that is contrary to the "central dogma" of genetics (DNA – RNA – protein). The Office has identified a single example in which mRNA expression does not necessarily dictate translation of a polypeptide. The Office has not provided evidence that one more likely than not would fail to expect translation of the PHELIX protein in accordance with the central dogma of genetics.

Applicant further asserts that example 6 demonstrates expression of a cDNA encoding PHELIX in transfected 293T cells and detection of PHELIX by antibodies directed against PHELIX protein.

Applicant further submits the Declaration by Dr. R.S. Hubert, asserting that based on the mRNA expression of PHELIX, PHELIX protein is expected to be useful for detection and treatment of cancers expressing PHELIX. The Declaration provides further evidence, wherein immunohistochemical data show the detection of PHELIX protein in the cytoplasm of 293T cells transfected with an expression vector containing DNA encoding PHELIX and not in untransfected 293T cells.

Applicant's arguments set forth in paper No.13 have been considered but are not deemed to be persuasive for the following reasons:

The Declaration by Dr. R.S. Hubert is acknowledged.

It is unpredictable that PHELIX protein is expressed in cancer cells. Contrary to Applicant's assertion, the reference by Fu et al is not an exception. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Further, expression of a cDNA encoding PHELIX in transfected 293T cells and detection of PHELIX by antibodies directed against PHELIX protein in transfected 293T cells and not in non-transfected cells is an artificial condition and could not be used to predict expression of PHELIX proteins in cancer cells.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

New claims 68-69, 71-72 are rejected under 35 USC 101 pertaining to lack of a clear written description remains for reasons already of record in paper No.10.

Applicant asserts that the specification provides guidance in the selection of regions which may tolerate variability, the identification of conserved regions and information regarding the function of particular portions of the protein. In particular, the specification identifies the basic helix loop helix domain and two nuclear localization signals. The structural and functional feature of PHELIX protein are discussed at pages 8-9 in the specification. Further, PHELIX is shown to express in the nuclei (figure 9), expected for a protein having a nuclear localization signal and a basic helix loop helix.

Applicant further asserts that examples 13, 14 at pages 50-55 include several examples of fragments or polypeptides having a high homology to PHELIX protein.

Applicant also asserts that the statement that structural features that could distinguish the compounds in the genus from others are missing in the disclosure is not true. All elements of previous claims 1-4 are structurally determined with regard to specific amino acid sequence of SEQ ID NO:2. The specification describes structural features of PHELIX proteins and polypeptides, including fragments of the amino acid

sequence described in SEQ ID NO:2. The specification indicates that PHELIX polypeptides of the invention exhibit properties of the PHELIX protein, such as the ability to elicit the generation of antibodies which specifically bind an epitope associated with the PHELIX protein.

Applicant's arguments set forth in paper No.13 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that there is only Example 13, at pages 40-41, but not example 14. Further, pages 50-55 do not exist. Moreover, Example 13 only describes the expression of PHELIX protein in a subcellular fraction, i.e. in the nuclei, of transfected 293T cells. Example 13, and the specification do not describe any example of fragments or polypeptides having a high homology to PHELIX protein, wherein the sites of deletion or addition or substitution, or the amino acids that are deleted or added or substituted are identified. Thus although the specification describes structural features of PHELIX proteins and polypeptides, including fragments of the amino acid sequence described in SEQ ID NO:2, the specification does not describe the features of the claimed variants.

Further, regions which could not be changed and are necessary for the function of PHELIX protein are not identified, because the function of PHELIX protein is not known. The specification discloses that the claimed bHLH region from PHELIX protein has 60% and 70% similarity with the bHLH domain Max, a transcriptional factor, in rat and Mxi, a transcriptional factor in zebrafish, respectively (figure 3). Although the specification identifies regions that are homologous to the basic helix loop helix domain and nuclear localization signals, it is not necessarily that PHELIX protein function as a

transcriptional factor, because one could not base solely on sequence homology to predict the function of a protein. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution

will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 40% and 30% dissimilarity to Max and Mxi, respectively, the function of the SEQ ID NO:2 polypeptide, or PHELIX protein could not be predicted, nor would it be expected to be the same as that of Max or Mxi. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more

difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2).

Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, . Clearly, with 40% and 30% dissimilarity to Max and Mxi, respectively, the function of the SEQ ID NO:2 polypeptide,

or PHELIX protein could not be predicted, nor would it be expected to be the same as that of Max or Mxi.

Moreover, the presence of possible nuclear localization signals does not predict the function of the PHELIX protein. Further, the PHELIX localization data seem to be contradictory. Whereas the specification discloses that PHELIX protein seems to be located only in the nucleus of transfected cells (figure 9), the Declaration discloses that the PHELIX protein seems to be located in the cytoplasm.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

New claims 54-77 are rejected under 35 USC 101 pertaining to lack of support from a specific and/or substantial utility remains for reasons already of record in paper No.10.

Applicant asserts that in view of the cancellation of claims 1-4, 13, 51 and 52 the rejection is moot.

Applicant's arguments set forth in paper No.13 have been considered but are not deemed to be persuasive for the following reasons:

Rejection remains for the same reasons set forth above under 101 rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 56-70, 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 56-57, 60-63, 77 are drawn to a polypeptide of at least 10 or 15 contiguous amino acids of SEQ ID NO:2, wherein the polypeptide is recognized by an antibody that specifically binds to SEQ ID NO:2. Said polypeptide comprises amino acid residues 140-154, 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2.

Claims 58, 59, 64-67 are drawn to a polypeptide of at least 10 or 15 contiguous amino acids of SEQ ID NO:2, wherein the polypeptide binds MHC class I or II molecules and is recognized by a T cell that specifically recognizes SEQ ID NO:2. Said polypeptide comprises amino acid residues 140-154, 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2.

Claims 68-70 are drawn to a polypeptide that is at least 90% identical to SEQ ID NO:2 over the entire length of SEQ ID NO:2, wherein the polypeptide is recognized by an antibody that specifically binds to SEQ ID NO:2.

Claims 56-57, 60-61, 77 encompass a polypeptide of at least 10 or 15 of "any contiguous amino acids" of SEQ ID NO:2, which is the epitope of an antibody that specifically binds to SEQ ID NO:2. Claims 62-63 encompass a polypeptide comprising amino acid residues 140-154, 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2, wherein said polypeptide is specific for SEQ ID NO:2 and is the epitope of an antibody that specifically binds to SEQ ID NO:2.

Claims 58, 59, 64-65 encompass a polypeptide of at least 10 or 15 contiguous amino acids of SEQ ID NO:2, wherein the polypeptide is specific for SEQ ID NO:2,

binds MHC class I or II molecules and is recognized by a T cell that specifically recognizes SEQ ID NO:2. Claims 66-67 encompass a polypeptide comprising amino acid residues 140-154, 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2, wherein said polypeptide is specific for SEQ ID NO:2, binds MHC class I or II molecules and is recognized by a T cell that specifically recognizes SEQ ID NO:2.

The specification discloses that the amino acid sequence HSSKEKLRRERIKYC, which is the same as amino acid residues 140-154 of SEQ ID NO:2, as shown in figure 2, produces a polyclonal antibody in rabbit, that has specificity for PHELIX or SEQ ID NO:2 (p.35 bridging p.36). No further disclosure of antibodies to any other fragments of SEQ ID NO:2 is found in the specification. In addition, there is no data showing that the claimed antibody produced by the amino acid sequence HSSKEKLRRERIKYC is actually specific for SEQ ID NO:2.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is unpredictable that PHELIX protein exists in nature, *supra*, and even if PHELIX protein exists in nature, it is unpredictable that a polypeptide of at least 10 or 15 of "any contiguous amino acids" of SEQ ID NO:2, or amino acid residues 140-154, 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2 are the epitopes of antibodies that specifically binds to SEQ ID NO:2. Although the amino acid sequence HSSKEKLRRERIKYC or amino acid residues 140-154 could be used to produce polyclonal antibodies that bind to SEQ ID NO:2, it is questionable that said antibodies are specific for SEQ ID NO:2. From figure 2, amino acid residues 140-154 represent part of a fragment that is homologous to the well known basic Helix Loop Helix (bHLH)

domain of transcriptional factors (figure 2 legend, figure 2, and page 9, second paragraph). Since antibody cross-reactivity is well known in the art, and since an antibody could be specific or selective for only one or two amino acids epitopes, wherein said one or two amino acids could be shared by unrelated proteins, one would have expected that the antibody to amino acid residues 140-154 would cross-react and bind to the bHLH domain of transcriptional factors, or any other unrelated sequences that share some common amino acids with amino acid residues 140-154. Banki et al, 1994, JBC, 269(4): 2847-51, teach that an antibody against human transaldolase could bind to yeast transaldolase which is about 58% homologous with human transaldolase, i.e. an antibody could bind to a polypeptide at least with 58% homology to its antigen. From sequence homology search, amino acid residues 140-154 are 100% similar to a transcriptional factor from amino acid 6 to 11 (MPSRCH search report, us-09-389-000-2-copy-140-154.rsp, page 7), and are 100% similar to a peptide signal sequence, from amino acid 2 to 6 (MPSRCH search report, us-09-389-000-2-copy-140-154.lim.rag, page 2.). Thus based on the above information, one would have expected that the antibody to amino acid residues 140-154 would cross-react and bind to the bHLH domain of transcriptional factors, or any other unrelated sequences that share some common amino acids with amino acid residues 140-154.

In addition, expression of a cDNA encoding PHELIX in transfected 293T cells and detection of PHELIX by antibodies directed against PHELIX protein in transfected 293T cells and not in non-transfected cells is an artificial condition and could not be used to interpreted that the claimed antibody to amino acid residues 140-154 is specific

for PHELIX protein. In transfected cells, usually the proteins are artificially overexpressed, which is not the same conditions as in cancer cells. Thus, due to the possible masking effect of an artificially overabundant amount of PHELIX protein as compared to any other proteins in the transfected cells, detection of PHELIX protein does not necessarily mean that the antibodies to PHELIX protein is specific for PHELIX protein, and would not detected other unrelated proteins sharing some homology with amino acid residues 140-154 in cancer cells.

Further, except for the antibody against amino acid residues 140-154, it would not be possible to determine with any predictability whether the antibodies produced from a polypeptide of at least 10 or 15 of "any contiguous amino acids" of SEQ ID NO:2, or amino acid residues 134-150, 134-189, 140-163, 140-189 or 163-169 of SEQ ID NO:2 actually bind to SEQ ID NO: 2. It is well known in the art that when using synthetic amino acid sequences as immunogens to develop antibodies, one cannot be certain how well exposed such a peptide is nor how immunogenic it is. In other words, it is unpredictable that the claimed fragments, or sequences that are specific for SEQ ID NO:2 are exposed on the surface of SEQ ID NO:2. Roitt et al, 1998, Immunology, 4th ed, Mosby, London teach that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (p.7.7-7.8). Furthermore, this does not take into account the 3

dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. Peptides or synthetic antigens cannot effectively substitute for the natural tertiary and quarterary structure of a protein in a physiological situation. Further, there is no teaching in the specification of which part of the protein should be used to produce antibodies which will bind specifically to SEQ ID NO:2.

Moreover, as written, claims drawn to short peptide sequences, which are also part of the sequence of SEQ ID NO: 2, encompass claims to defining epitopes of a polypeptide. However, there is no teaching in the specification of whether or not the epitopes are linear or comprise 3-dimensional structures. Herbert et al. (The Dictionary of Immunology, Academic Press, 4th edition, 1995, p.58) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by the claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the

molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Since the specification has not identified which amino acids and or polypeptide fragments are critical or essential characteristics of the epitope, it would not be predictable, to one of relative skill in the art, that such methods employing agents would be specific for any epitopes on SEQ ID NO: 2.

Moreover, there is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to stimulate and generate CTLs. There is insufficient guidance regarding selection of peptides that meet the instant criteria of generating CTLs that kill tumor cells. In other words, not any peptide from a protein deduced from SEQ ID NO:2 is able to bind to HLA class I, and to stimulate and generate CTLs. Roitt I et al, *supra*, page 7.9, teach that only a minority of peptide fragments from a protein antigen are able to bind to a particular MHC molecule.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the claimed immunogenic fragments. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the encompassed fragments. Therefore, undue experimentation would be required to enable the claims as written.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

New claims 68-69, 71-72 are rejected under 35 USC 101 pertaining to lack of enablement for a polypeptide that is 90% identical to SEQ ID NO:2 remains for reasons already of record in paper No.10.

Applicant asserts that the specification provides ample guidance to confirm whether the candidate variant has the biological activity of PHELIX protein. The specification discloses methods of identifying PHELIX proteins and variants using antibodies directed against PHELIX.

Applicant s arguments set forth in paper No.13 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the biological activity of PHELIX protein is not known, *supra*. Further, proteins that react with the claimed antibodies would not necessarily have the same biological activity of PHELIX protein, because the claimed antibodies are not specific for PHELIX protein, and the detected proteins could be unrelated proteins sharing with PHELIX protein a common fragment (see the new 112, first paragraph rejection set forth above).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 6, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600